Celiac Disease is Misdiagnosed Based on Serology Only in a Substantial Proportion of Patients

Stephan R. Vavricka, MD,† Teresa Stelzer, MD,† Jaqueline Lattmann, MS,† Matthias Stotz, MS,† Romina Lehmann, MS,† Jonas Zeitz, MD,* Michael Scharl, MD,* Benjamin Misselwitz, MD,* Daniel Pohl, MD,* Michael Fried, MD,* Radu Tutuian, MD,‡ Alessio Fasano, MD,§ Alain M. Schoepfer, MD,‖ Gerhard Rogler, MD, PhD,* Luc Biedermann, MD,* and Thomas Greuter, MD**

Background: Although the diagnostic process in celiac disease (CeD) has been addressed in several international guidelines, little is known about the actual proceeding in current clinical practice. This study investigated the initial presentation, the diagnostic process, follow-up evaluations, and adherence to a gluten-free diet in CeD patients in a real-life setting in Switzerland from a patient's perspective.

Methods: We performed a large patient survey among unselected CeD patients in Switzerland.

Results: A total of 1689 patients were analyzed. The vast majority complained of both gastrointestinal and nonspecific symptoms (71.5%), whereas 1.8% reported an asymptomatic disease course. A total of 35.8% CeD patients were diagnosed by a nongastroenterologist. The diagnostic process differed between nongastroenterologists and gastroenterologists, with the latter more often using duodenal biopsy alone or in combination with serology (94.7% vs. 63.0%) and nongastroenterologists more frequently establishing the diagnosis without endoscopy (37.0% vs. 5.3%, $P < 0.001$). Follow-up serology after 6 months was performed only in half of all patients (49.4%), whereas 69.9% had at least 1 follow-up serology within the first year after diet initiation. About 39.7% had a follow-up endoscopy with duodenal biopsies (after a median of 12 mo; range, 1 to 600 mo). The likelihood of receiving any follow-up examination was higher in patients initially diagnosed by a gastroenterologist.

Conclusions: A significant proportion of CeD patients are diagnosed by nongastroenterologists. Under the diagnostic lead of the latter, more than a third of the patients receive their diagnosis on the basis of a positive serology and/or genetics only, in evident violation of current diagnostic guidelines, which may lead to an overdiagnosis of this entity.

Key Words: celiac disease, diagnostic work-up, serologic testing, duodenal biopsy, gluten-free diet

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Celiac disease (CeD) is a systemic immune-mediated disorder triggered by gluten intake in genetically predisposed patients.[1] CeD affects 0.6% to 1.0% of the general population worldwide,[2–7] with a higher prevalence among patients with other autoimmune disorders including type 1 diabetes mellitus or thyroid diseases and genetic disorders such as Turner or Down syndrome.[8] Regional differences among comparably developed countries and a female preponderance for CeD have been described; however, the reasons for these remain unclear.[9,10] Increasing prevalence in developing countries seems to be attributable to a western diet, changes in wheat production, better diagnostics, and increased awareness of the disease.[1] Serologic screening studies suggest a high number of clinically unrecognized CeD cases;[2,9] accordingly, in most patients, CeD remains undiagnosed.

CeD remains a diagnostic challenge due to the broad range of possible clinical manifestations. In contrast, CeD symptoms differ according to age at manifestation: infants more often suffer from diarrhea and failure to thrive,[11] whereas adolescents may complain of extraintestinal manifestations such as a short stature or neurological symptoms.[12] However, typical gastrointestinal symptoms, among which diarrhea is the most frequently reported, are encountered in only half of all cases.[13] Furthermore, some CeD cases are suspected by laboratory findings only such as elevated liver enzymes or otherwise unexplained iron-deficiency anemia. Moreover, CeD may be incidentally diagnosed during upper endoscopies performed for other indications.

Current guidelines recommend serology and duodenal biopsy for CeD diagnosis with biopsy considered as its mainstay.[14] Patients with a high clinical suspicion of CeD

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From the *Division of Gastroenterology and Hepatology, University Hospital Zurich; †Division of Gastroenterology and Hepatology, Triemli Hospital Zurich, Zurich; ‡Division of Gastroenterology and Hepatology, Spital Tiefenau, Bern; ‖Division of Gastroenterology and Hepatology, University Hospital Lausanne—CHUV, Lausanne, Switzerland; and §Pediatric Gastroenterology and Nutrition, MassGeneral Hospital for Children, Boston, MA.
S.R.V., T.S., and T.G. share co-first authorship.
L.B. and T.G. share co-last authorship.
S.V.R. and T.S. were responsible for the study design, acquisition and analysis of data, and drafting of the manuscript. J.L., M.St., and R.L. were responsible for acquisition and analysis of data. J.Z., M.Sc., B.M., D.P., M.F., R.T., A.F., A.M.S., and G.R. critically revised the manuscript. L.B. and T.G. were responsible for the study design, acquisition and analysis of data, and drafting of the manuscript.
The authors declare that they have nothing to disclose.
Address correspondence to: Stephan R. Vavricka, MD, Division of Gastroenterology and Hepatology, Triemli Hospital Zurich, Birmensdorferstrasse 497, Zurich 8063, Switzerland (e-mail: stephan.vavricka@triemli.zuerich.ch).
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should undergo endoscopy and duodenal biopsy regardless of the initial serologic testing. As an exception, recently published European pediatric guidelines suggest a place for CeD diagnosis without the need for duodenal biopsies in the presence of typical symptoms, high serologic titers, and predisposing human leukocyte antigen (HLA) genotypes (DQ2 and/or DQ8).[15] However, this practice remains highly controversial outside Europe[16] and among some European pediatric gastroenterologists.[17] It seems evident that CeD diagnosis has to be established with high accuracy in every patient considering its pronounced consequences for patients' everyday life: a gluten-free diet (GFD) with life-long elimination of wheat, rye, and barley imposes strong dietary restrictions and has social and economic consequences. In addition, incorrectly diagnosed CeD patients triggers significant health care costs due to unnecessary follow-up visits. Because of the need of a very high diagnostic threshold, clinical improvement after implementation of GFD is not considered sufficient to secure the diagnosis of CeD.[18] Furthermore, given that histologic findings in CeD are characteristic, but nonspecific,[19] some experts even recommend the repetition of duodenal biopsies after 1 year of dietary therapy.[14] However, how these sometimes conflicting expert recommendations regarding CeD diagnosis are implemented in clinical practice remains unclear. Close follow-up especially in the first year after diagnosis is recommended for all CeD patients. Assessing adherence to GFD is key and consists of 4 steps: (i) clinical assessment of symptoms, (ii) a dietetic review, (iii) serum antibodies, and (iv) possibly follow-up biopsies, which are recommended if the condition does not respond to GFD or if patients are at an increased risk of lymphoma.[14] Considering the evidence that adherence to GFD and mucosal healing can prevent CeD complications, such a thorough follow-up of CeD patients seems essential.[20] However, compliance with these recommendations in a real-life setting has not been addressed.

This study investigates the initial presentation, the diagnostic process, follow-up evaluations, and adherence to GFD in CeD patients in a real-life setting in Switzerland from a patient's perspective.

MATERIAL AND METHODS

Study Design

This large patient survey collected information about CeD presentation, the diagnostic process, treatment, and adherence to GFD on the basis of an exclusive patient perspective. The call to CeD patients was made through announcements in print news of the Celiac Community Foundation of the German-speaking part of Switzerland and on its website. Patients or their caregivers (for pediatric patients) were prompted to report their own case to the database using a standardized questionnaire. Patient answers and all additional data were anonymized. The study was presented to the local Ethics committee and the need for approval was waived due to anonymized data collection.

Patients and Data Collection

All patients diagnosed with CeD were eligible for inclusion in this study. Data were exclusively collected using a questionnaire, which included sections about: (1) patient demographic data, (2) disease characteristics (first symptoms, age at disease onset) and diagnostic process, (3) GFD and adherence to therapy, (4) disease course and follow-up visits after implementation of dietary restrictions. Clinical remission at follow-up visits was defined as the complete absence of any CeD symptom. For comparison between adult and pediatric study populations, adults were defined as patients above the age of 18 years according to other CeD studies.[21]

Statistical Analysis

For all statistical analyses, IBM software SPSS version 23.0.0 (2014 SPSS Science Inc., Chicago, IL) was used. Categorical data are summarized as the percentage of the group total. Comparisons between categorical data were performed using the χ^2 test or the Fisher exact test in case of a small sample size ($n < 10$). A 2-sided P-value of < 0.05 was regarded as statistically significant. For a more detailed subgroup analysis, patients who were younger than 18 years at CeD diagnosis were excluded.

RESULTS

Patient Demographics

From a total of 3800 printed questionnaires, 1689 (44.4%) were returned and finally analyzed. Demographic data of the study population have been published elsewhere: 1284 participants were female (76%), the mean age was 41.3 years (range, 0 to 92 y) with a mean age at CeD diagnosis of 31.1 years (range, 0 to 83 y),[22] and 449 patients (26.6%) were below 18 years at the time of CeD diagnosis.

First Presentation and Diagnosis of CeD

Only 15.3% of the patients reported isolated gastrointestinal symptoms as their initial presenting symptoms. The vast majority complained of both gastrointestinal and nonspecific symptoms (71.5%). About 1.8% reported an asymptomatic disease course. Among all symptoms, flatulence, abdominal pain, and diarrhea were the most frequently reported with at least one of them was present in > 50% of all patients (Supplementary table 1, Supplemental Digital Content 1, http://links.lww.com/JCG/A282).

Most patients first presented to a nongastroenterologist (75.1%). However, the final diagnosis of CeD was established in only 35.8% of the cases by a nongastroenterologist (Table 1). Diagnostic delay by physicians tended to be shorter if patients presented to a gastroenterologist first (mean 31.6 vs. 41.3 months, median 1.0 vs. 5.0 months, $P = 0.093$). About 16.4% of all patients were diagnosed on the basis of serology and/or genetics (HLAII DQ2 and DQ8), whereas in the vast majority of the cases, the diagnosis was established by a combination of serology and duodenal biopsy (46.9%) or biopsy alone (31.9%). In the remaining cases, diagnostic steps were not specified. Under the diagnostic lead of nongastroenterologists, the diagnostic process differed significantly compared with that of gastroenterologists: Gastroenterologists more often used duodenal biopsy alone or in combination with serology (94.7% vs. 63.0%, $P < 0.001$), whereas diagnosis was more frequently established without endoscopy by nongastroenterologists (37.0% vs. 5.3%, $P < 0.001$). Differences remained significant if only adult patients (18 y or above at diagnosis) were analyzed (95.6% vs. 58.5%, and 41.5% vs. 4.4%, $P < 0.001$).

TABLE 1. Diagnostic Work-up in Adult Patients (18 y or Above at Diagnosis) and in All Patients

Diagnostic Modality	Diagnosis by a Nongastroenterologist (N = 354) (100%) [n (%)]	Diagnosis by a Gastroenterologist (N = 758) (100%) [n (%)]
Adult patients (18 y or above at diagnosis)		
Serology alone	126 (35.6)	26 (3.4)
EGD and biopsy alone	51 (14.4)	346 (45.6)
Serology and EGD/biopsy	156 (44.1)	379 (50.0)
Others (genetics alone, serology and genetics)	21 (5.9)	7 (0.9%)
	Genetics (3), genetics and serology (6), not specified (12)	Genetics (2), genetics and serology (2), not specified (3)
		$P < 0.001$ (biopsy vs. nonbiopsy)
	N = 592 (100%) [n (%)]	**N = 1006 (100%) [n (%)]**
All patients		
Serology alone	181 (30.6)	36 (3.6)
EGD and biopsy alone	105 (17.7)	430 (42.7)
Serology and EGD/biopsy	268 (45.3)	523 (52.0)
Others (genetics alone, serology and genetics)	38 (6.4)	17 (1.7)
	Genetics (5), genetics and serology (14), not specified (19)	Genetics (4), genetics and serology (8), not specified (5)
		$P < 0.001$ (biopsy vs. nonbiopsy)

EGD indicates upper endoscopy.

CeD Treatment and Follow-Up

GFD remains the mainstay of therapy as 97.7% of the patients reported having been treated by GFD. More than 3 of 4 patients (79.8%) received expert nutrition counseling. This counseling was more often prescribed if CeD diagnosis was established by a gastroenterologist (83.5% vs. 76.0%, $P = 0.001$). About 77.0% of all patients reported adhering always and 20.7% with only minor mistakes to a GFD. Patients who were only incidentally diagnosed with CeD tended to adhere to dietary treatment less than patients with symptoms at diagnosis (63.3% vs. 77.7%, $P = 0.06$). No difference regarding adherence to GFD was seen in patients with gastrointestinal symptoms compared with those with a nongastrointestinal presentation. Interestingly, younger patients (aged below 30 y) reported higher adherence than patients aged over 30 years (80.5% vs. 76.2% for adherence "always" to GFD, $P = 0.05$).

Follow-up serology after 6 months was performed in half of all patients (49.4%), whereas 69.9% had at least 1 follow-up serology within the first year after diet initiation. Serology results were infrequently reported; however, at least 19.3% had a positive serology after 6 months (53.8% missing) and 18.5% after 12 months (41.9% missing), respectively. About 39.7% of the patients had a follow-up endoscopy with duodenal biopsies (median duration after diet initiation 12 mo; range, 1 to 600 mo). In adult patients (18 y or above). follow-up serologies were more frequently performed if the CeD diagnosis was established by a gastroenterologist (at 6 mo 58.7% vs. 51.2%, $P = 0.032$, at 12 mo 62.6% vs. 51.6%, $P = 0.002$). In addition, follow-up biopsies were more often performed in adult patients diagnosed by a gastroenterologist compared with those who were initially diagnosed by a nongastroenterologist (54.0% vs. 44.9%, $P = 0.007$) (for details, see Figure 1).

About 43.7% of the patients reported complete clinical remission 6 months after GFD initiation. The proportion of complete remission was 59.4% after 12 months compared with 61.7% after 24 months. No difference regarding clinical remission was seen in those patients initially diagnosed by a gastroenterologist compared with those diagnosed by a nongastroenterologist, either at 6 months or at 12 and 24 months after CeD diagnosis. Similar results were seen if only adult patients were analyzed.

DISCUSSION

In this large patient survey, we report the presentation, diagnostic work-up, treatment by GFD, and follow-up evaluations in CeD from a patient's perspective. In contrast to actual CeD guidelines, up to one sixth of all CeD patients were diagnosed by serology only: reaching even 4 of 10 patients if diagnosis was established by non-gastroenterologists. Furthermore, we demonstrate a high frequency of nonspecific, nonclassical CeD symptoms and a mismatch between self-reported diet adherence and clinical remission rates.

In accordance to Rampertab et al[13] and other studies evaluating the presentation of CeD,[11] diarrhea and abdominal pain are among the most frequently reported CeD symptoms. However, >40% of our patients did not suffer from diarrhea, which is believed to be the classical CeD symptom. In addition, nonclassical gastrointestinal

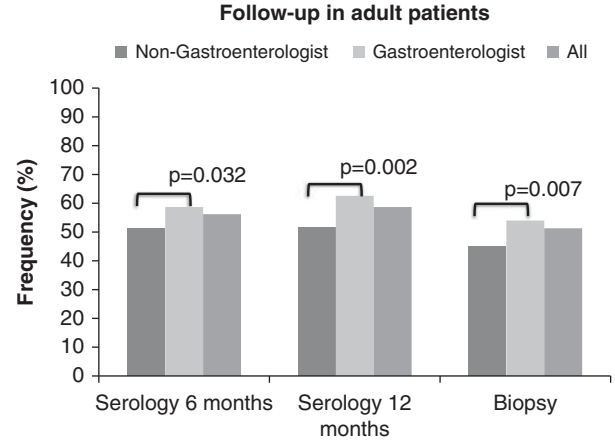

FIGURE 1. Follow-up evaluations in adult patients after diet initiation.

symptoms such as flatulence, constipation, nausea, or vomiting are frequently encountered. Only 15% presented with isolated gastrointestinal symptoms, underlining the crucial importance of awareness toward nonspecific CeD presentations such as fatigue or unexplained weight loss. Exceptional symptoms such as edema, skin lesions, migraine, or even paresthesia are not uncommon in our cohort; up to 1 of 10 patients presented with one of these symptoms. In any case, in our cohort, most patients recalled at least some presenting symptoms and an asymptomatic disease course was reported only by 2% patients. This number contrasts prior findings, for instance by Rutz et al,[23] suggesting a higher prevalence of asymptomatic CeD compared with symptomatic forms. Given the high frequency of nonspecific gastrointestinal and nongastrointestinal symptoms, CeD should also be considered in the absence of a classical presentation with diarrhea and abdominal pain. CeD screening in these patients will possibly uncover more CeD cases as seen in the study of Catassi et al.[24]

Importantly, we found that up to one sixth of all CeD patients received their diagnosis without endoscopic assessment on the basis of serology and/or genetics only. This apparent clinical practice contrasts current CeD diagnostic guidelines,[14] which consider upper endoscopy with duodenal biopsy as the mainstay in CeD diagnosis. Furthermore, we demonstrate that CeD without endoscopy was significantly more often diagnosed by nongastroenterologists. Almost 4 of 10 nongastroenterologists made a CeD diagnosis on the basis of serology and concomitant symptoms/signs only. If we further take into account that up to one third of the patients received their diagnosis by a nongastroenterologist, then in more than 200 patients (12%) CeD diagnosis was not established in accordance to diagnostic guidelines. In addition to that, even gastroenterologists did not follow diagnostic guidelines rigourously. In summary, >16% of all 1689 patients did not receive their diagnosis correctly. Biagi et al[25] have recently shown that in 61 of 180 patients who did not receive their CeD diagnosis correctly, the diagnosis of CeD could not be confirmed after reinvestigation. Thus, there may indeed be a substantial risk of overdiagnoses of the CeD entity and therefore unnecessary, lifelong dietary restrictions and follow-up evaluations. This finding has important clinical implications as implementing an accurate diagnostic process[14] might not only impact on individual patient's life but also safe health care costs.

The reported excellent adherence rate to GFD is >70% in our cohort. Our results agree with previous findings, although our adherence rates are definitely in the upper limit. In addition, self-reported adherence rates are notoriously higher than true adherence rates.[26] In the meta-analysis of Hall et al,[27] strict adherence rates measured by self-report ranged from 42% to 91%. In contrast to other studies, where the effect of age is unclear[28,29] or younger age even correlated with lower adherence,[30,31] we found that adult patients under 30 years of age show better adherence. In addition, symptomatic CeD patients tend to adhere better than those with an asymptomatic disease course, also contrasting prior findings.[27] In our cohort, high adherence rates to GFD contrast with the relatively lower rates of clinical remission of 50% at 6 months after diagnosis, although some increase was observed over the following 2 years. This mismatch may certainly be explained by a self-report assessment and therefore a possible misinterpretation of adherence to GFD by each individual patient, despite a relatively high proportion of patients receiving specialized nutrition counseling. Of note, such counseling was more often prescribed, if a gastroenterologist was involved in the CeD diagnosis and follow-up evaluations. In addition, follow-up examinations (serology, biopsy) were more often ordered/performed by gastroenterologists. However, both gastroenterologists and nongastroenterologists did not use them as recommended in expert guidelines. It remains unclear whether the more rigorous but imperfect follow-up by gastroenterologists impacts the clinical course of patients because neither adherence rates to GFD nor rates of clinical remission were higher in patients diagnosed and treated by a gastroenterologist compared with a nongastroenterologist.

Our study has several limitations: (i) exclusively relying on self-reports may have led to an overestimation of adherence rates. However, these rates are comparable to those in other studies[27] and verifying true adherence remains a challenge regardless of assessment by a physician. (ii) Because of the retrospective assessment of symptoms, our results are prone to recall bias. (iii) Another limitation may be the absence of external validation including physician assessment or chart review. Misperception of diagnostic steps may have led to an overestimation of CeD cases diagnosed without endoscopy and duodenal biopsy. However, the rates of missing values regarding the CeD diagnostic process are low [78/1689 (4.6%) in all patients; 6/1124 (3.2%) in adult patients], supporting an adequate patient perception. (iv) Another limitation is a possible selection bias due to exclusive inclusion of patients who were members of the Celiac Community Foundation of the German-speaking part of Switzerland. Patients with a symptomatic CeD course may more likely be members of this foundation, which is supported by the fact that asymptomatic CeD patients are underrepresented in this study.

In conclusion, more than 1 of 3 CeD patients are diagnosed by nongastroenterologists. Under the diagnostic lead of nongastroenterologists, more than a third of the patients receive their diagnosis on the basis of a positive serology and/or genetics only, in evident violation of current diagnostic guidelines.[14] This may lead to a substantial proportion of overdiagnoses and therefore unnecessary, potentially lifelong dietary restrictions as well as follow-up evaluations in these patients. In addition, nonspecific nonclassical symptoms—either gastrointestinal or nongastrointestinal—are frequent, and lack of diarrhea and/or abdominal pain should not delay diagnostic work-up.

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